

Adverse Events in HIV- infected Children on Antiretroviral Therapy at a Teaching Hospital in Lagos, Nigeria: A Retrospective Study

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Abstract

Background: Highly active antiretroviral therapy (HAART) program requires adequate monitoring of the potential adverse events to the antiretroviral (ARV) drugs. We investigated the ARV drug combinations prescribed for HIV- infected children and their suspected adverse events.

Methods: This is a retrospective and descriptive study involving HIV- infected children less than 15 years old who received treatment at the APIN clinic, Lagos University Teaching Hospital (LUTH) in Nigeria. The case files of 80 patients initiated on HAART, between January 2008 and December 2009, were reviewed. Their demographics, clinical details and medication use, the prescribed HAART regimen, and the suspected clinical and laboratory adverse events were extracted.

Results: The patients were female (46; 57.5%) preponderant with a median age of 3 (IQR: 1.1-6.0) years. Zidovudine- lamivudine- nevirapine (AZT-3TC-NVP) combination (74; 92.5%) was the most frequently prescribed first-line regimen. Thirty three patients changed their first-line HAART to abacavir-lamivudine-lopinavir boosted with ritonavir (ABC-3TC-LVP/r) (11; 33.3%), and zidovudine- lamivudine- abacavir- lopinavir boosted with ritonavir (AZT-3TC-ABC-LVP/r) (8; 24.2%) combinations. Of the 80 patients included in the study, 38(47.7%) experienced 142 adverse events. The most frequently experienced clinical adverse events were nevirapine-induced skin rashes (93; 65.5%), vomiting (19; 13.4%), and pallor (12; 8.5%). Macrocytosis (22/72; 30.6%), anaemia (6/72; 8.3%), and thrombocytopenia (2/72; 2.8%) were the commonest haematological adverse events associated with zidovudine.

Conclusions: The HAART regimens used for HIV-infected children in this study have a good safety profile. Their few adverse events suggest a need for prospective pharmacovigilance to effectively monitor the toxicities of ARV drugs.

Keywords: Adverse event; HIV; Children; Antiretroviral drug; Nigeria

Introduction

The burden of HIV is high globally as it remains the greatest health crisis facing the world today. There are approximately 34 million people currently living with HIV and nearly 30 million people have died of AIDS-related causes since the beginning of the epidemic [1,2]. The highest proportion of people living with HIV (97%) resides in low- and middle-income countries, particularly in sub-Saharan Africa [3].

Highly active antiretroviral therapy (HAART); defined as a combination of three or more antiretroviral (ARV) agents taken concurrently to suppress HIV replication, represents the current standard of care of antiretroviral therapy for children infected with HIV [4]. This strategy evolved from the recognition that continual treatment of HIV infection with only one or two ARV agents would typically result in rapid treatment failure and development of ARV resistance which may compromise future therapeutic options [4,5].

Treatment failure and toxic effects of ARV drugs are the major reasons for changing therapy in children [6] and adults [7] in resource-poor countries. In addition to availability of ARV drugs, an effective HAART program requires adequate monitoring of the potential adverse events to the ARV drugs. Several strategies, including continual development of new ARV agents, and better understanding and

management of adverse effects of the currently available drugs, have been implemented to improve treatment duration [8]. Differentiating between adverse consequences of HIV infection and toxicities of drugs used in its management may be challenging. However, following the use of a combination of ARV drugs, some distinct adverse drug events have been reported as case reports [9,10].

Despite a wide range of clinical and epidemiological studies of HIV/AIDS in Nigeria [11-13], there is scarce information on the adverse events that occurred following the use of ARV drugs, particularly in children. Therefore, this study aimed to evaluate the ARV drug

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combinations prescribed for HIV-infected children at the APIN clinic, LUTH in Nigeria. It also aimed to document the suspected adverse events to the ARV drugs.

Methods

Patients and settings

This retrospective descriptive study was conducted at the Lagos University Teaching Hospital (LUTH) in Nigeria and involved HIV-infected children who had been initiated on HAART and were receiving treatment at the *AIDS Prevention Initiative in Nigeria* (APIN) clinic at LUTH, between January 2008 and December 2010. The APIN clinic at LUTH is one of the United States Presidential Emergency Plan for AIDS Relief (PEPFAR) funded centres for HIV relief program. The clinic holds every Monday to Friday, between 8 am and 4 pm.

On the average, about 350 old and new HIV-infected adults and children are attended to daily at the APIN clinic. A total of 18 doctors; comprising of 4 consultants, 8 residents, and an average of 6 house officers attend to the children living with HIV during their visits to the APIN clinic. The consultants usually attend to all newly registered patients while the residents follow up the old cases and discuss each case with the consultants before taking new decisions on the patients' management. The house officers are involved in recording the results of laboratory investigations, as well as measuring and recording of the anthropometries of the patients. They also assist in filling the HAART prescription forms for the patients. ARV drugs prescribed to the patients on HAART enrolment are dispensed at the pharmacy free of charge by a paediatric pharmacist.

The study involved children who were less than 15 years of age, had been initiated on HAART between January 2008 and December 2009, and had at least one follow up clinical visit after commencing HAART between December 2009 and December 2010. All cases of death, incomplete records of the HAART, and complete default from the clinic after commencing HAART between December 2009 and December 2010, were excluded. Eligibility for HAART was based on the WHO guidelines [4]. Once eligible for ARVs, all patients are initiated on a HAART consisting of two nucleotide reverse transcriptase inhibitors (NRTIs- zidovudine (AZT)/lamivudine (3TC), or abacavir (ABC)/3TC) and one non-nucleotide reverse transcriptase inhibitors (NNRTI- nevirapine (NVP) or efavirenz (EFV)). Any ARV regimen outside these groups is classified as others. Thereafter, the patient was reviewed monthly for two months. At each appointment, adherence counseling was provided. The patient was subsequently given monthly prescriptions if found tolerant and adherent to the medication. Baseline CD4+, haematology and chemistry test were conducted for all patients and follow up laboratory test scheduled at 3 months and 6 months or as determined by the doctor.

During follow up adherence was assessed monthly by self-report of the primary caregiver (for children <6 years) or the patient (children ≥ 6 years). A treatment interruption due to poor adherence was defined as three or more consecutive missed daily doses of ARV medications in a treatment month after enrolment on HAART. Treatment failure that resulted in a change in HAART regimen was defined as a viral load greater than 5000 copies of HIV RNA/mL, for greater than 6 months, and resulting in an immunological decline [14].

Data abstraction

Eligible cases were identified through the main register obtained from the medical record of the APIN clinic. One of the researchers

reviewed each case file. Using a self-designed form for the study, he extracted data on gender, weight, height, mode of contracting HIV, presenting symptoms, co-morbid diseases and inter-current infections at presentation and follow up, co-administered drugs, and the ARV drug regimen prescribed for each patient.

The nutritional status of each patient was determined from the WHO child growth standards based on length or height, weight and age [15]. The nutritional status were classified as normal ($+3SD \leq Z \leq -1SD$), moderate malnutrition ($-1SD \leq Z \leq -2SD$), and severe malnutrition ($Z \geq -3SD$). The lead researcher corroborated the information previously extracted by further reviewing each case file. Where there were disagreements, the opinion of the third researcher superseded. The laboratory investigations of each patient, before enrolment on HAART (baseline) and during follow up (after enrolment on HAART) for the first 12 consecutive months, were also extracted. The laboratory investigations included the viral load, CD4+ count, haematological profile, and biochemical profile (blood chemistries, liver function test, and lipid profile). The results of the laboratory investigations were compared with the reference values according to the WHO's guidelines for the management of HIV-infection [1].

For those patients with changes in their first-line HAART regimen, the prescribed second-line regimen and the indications for the change were also extracted from their case files.

Patient assessment for adverse events to ARV drugs

Most of the potential adverse events to each ARV drug may mimic the presenting symptoms of HIV infection, thus making assessment of the patients for adverse events very challenging. We assessed clinical adverse events to the ARV drugs based on an increase in the severity of the presenting symptoms, presence of new symptoms after enrolment on HAART, known adverse events to each ARV drug documented in the WHO's HIV treatment guidelines for children [4], and rare adverse events to ARV drugs published as case reports. Laboratory adverse events were determined based on the abnormalities observed in the laboratory results before and after enrolment on HAART regimen with reference to the WHO's treatment guidelines [4].

Ethical issues

The study protocol was approved by the ethics committee of LUTH. The patients' data were de-identified and all cases treated anonymously.

Statistical analyses

All data from the medical records were coded and results presented as median and inter-quartile range (IQR), mean with standard deviation (mean \pm S.D), and frequency distribution with percentage. Statistical analysis on the results was performed using the Statistical Package for the Social Sciences (SPSS), version 16. Comparisons between the baseline and follow up data were made using the independent t-test at a significance level of $p < 0.05$.

Results

Demographics of the patients

One hundred and thirteen (113) patients were receiving care at the APIN clinic during the study period but only 80 were eligible for inclusion in the study. Of those eligible for inclusion in the study, 38(47.5%) experienced at least an adverse event to the ARV drug combinations prescribed. The demographics of the patients are presented in Table 1. More females (46; 57.5%) than males (34; 42.5%)

Patient characteristics	Patient population (N=80)
Median age, years (IQR)	3 (1.1-6.0)
Gender	
Male	34 (42.5%)
Female	46 (57.5%)
Nutritional status at first presentation	
Normal (+3SD ≤ Z ≤ -1SD)	50 (62.5%)
Moderate malnutrition (-1SD ≤ Z ≤ -2SD)	12 (15.0%)
Severe malnutrition (Z ≥ -3SD)	18 (22.5%)
Mode of Contracting HIV infection	
Mother-to-child transmission	47 (58.8%)
Not documented	22 (27.5%)
Unknown	8 (10.0%)
Blood transfusion	3 (3.8%)
Co-morbid disease and inter-current infection	
Malaria	53 (66.3%)
Pneumonia	18 (22.5%)
Tuberculosis	9 (11.3%)
Sepsis	1 (1.3%)

Table 1: Patients' Demographics.

ARV characteristics HAART regimen on enrolment	Patient population N=80
AZT-3TC-NVP	74 (92.5%)
AZT-3TC-EFV	5 (6.3%)
AZT-3TC-ABC-LPV/r	1(1.3%)
Change in HAART regimen	N=80
Yes	33 (41.3%)
No	47 (58.7%)
New HAART regimen	n=33
ABC-3TC-LPV/r	11(33.3%)
AZT-3TC-ABC-LPV/r	8 (24.2%)
AZT-3TC-ABC-ddl-LPV/r	5 (15.2%)
ABC-3TC-NVP	4 (12.1%)
AZT-ABC-LPV/r	3 (9.1%)
AZT-3TC-LPV/r	2 (6.1%)
Reason for changing HAART regimen	n=33
Poor adherence and therapeutic failure	29 (87.9%)
Therapeutic failure only	2 (6.1%)
Adverse drug reaction	1(3.0%)
Poor adherence only	1(3.0%)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs) include: Zidovudine (AZT), Lamivudine (3TC), Abacavir (ABC), and Didanosine (ddl). Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) include: Nevirapine (NVP) and Efavirenz (EFV). Protease Inhibitor (PI): Lopinavir boosted with Ritonavir (LPV/r)

Table 2: Types of antiretroviral drug regimen prescribed for HIV children at APIN clinic, LUTH.

were infected with HIV. Majority of the patients (50; 62.5%) were of normal nutritional status and infected via mother-to-child route of transmission (47; 58.8%).

Prescribed HAART regimen

Table 2 shows the types of HAART regimen prescribed for the patients. Upon enrolment on HAART, the majority of the patients (74; 92.5%) were initiated on a regimen of zidovudine- lamivudine-nevirapine (AZT-3TC-NVP) combination. A significant proportion of the patients (33; 41.3%) had a change in HAART regimen after their initial enrolment on a first-line regimen. Poor adherence and therapeutic failure (29/33; 87.9%) were the main reasons for changing HAART regimen. Nearly all the patients (32/33; 97%) who switched

Drugs	Number of patients using the drugs (%) (N=80)
Co-trimoxazole	67 (88.8%)
Artemisinin based combination therapies	47 (58.8%)
Cefuroxime	35 (43.8%)
Amoxicillin + clavulanic acid	30 (37.5%)
Multivitamins	29 (36.3%)
Paracetamol	26 (32.5%)
Ascorbic acid	24 (30.0%)
Chlorpheniramine	20 (25.0%)
Amoxicillin	19 (23.8%)
Erythromycin	18 (22.5%)
Ampicillin + cloxacilin	15 (18.8%)
Fluconazole	13 (16.3%)
Ketotifen	10 (12.5%)
Loratadine	9 (11.3%)
Metronidazole	7 (8.8%)
Prednisolone	7 (8.8%)

Table 3: Frequently used drugs to treat co-morbid conditions, opportunistic and inter-current infections in HIV-infected children on ARV drugs.

Onset of AEs from ART initiation	n (%) [Total AEs=142]
0-3 months	77 (54.2)
3-6 months	38 (26.8)
6-9 months	21 (14.8)
9-12 months	6 (4.2)
AEs distribution by age	
1-6 years	23 (60.5)
7-12 years	10 (26.3)
>12 years	5 (13.2)
AEs distribution by gender	
Male	13 (34.2)
Female	25 (65.8)

Table 4: Onset and distribution of adverse events (AEs) to antiretroviral drugs.

their HAART regimen did so after a year of commencing the first-line regimen.

Co-medications for HIV-infected children on ARV drugs

A wide range of medicines were co-administered to the patients while on HAART. The medicines were used for treating co-morbid conditions, opportunistic infections, or inter-current infections. Tuberculosis (9; 11.3%) was the commonest opportunistic infection treated in the patients (Table 1). It was treated with a combination of rifampicin-isoniazid-pyrazinamide for an average of six months before the patients were initiated on HAART regimen. Malaria (56; 66.3%), followed by pneumonia (18; 22.5%), were the most frequent inter-current infections treated in the patients (Table 1). The list of medicines frequently used to treat co-morbid conditions, and opportunistic or inter-current infections is presented in Table 3. Co-trimoxazole (67; 88.8%); prophylactically used against *Pneumocystis jiroveci*, was the most frequently prescribed medicine. This was followed by the antimalarial drug, artemisinin based combination therapies (ACTs) (47; 58.8%).

Suspected clinical adverse events to ARV drugs

Table 4 shows the onset and distribution of adverse events to the HAART regimens used for the patients. Majority of the adverse events (77; 54.2%) occurred early (within 3 months) after initiation of the HAART regimens. Young children (23; 60.5%) experienced more adverse events than older children and adolescents (15; 39.5%). More

Specific AE by organ system	AZT-3TC-NVP	AZT-3TC-EFV	ABC-3TC-NVP	AZT-3TC-LPV/r	ABC-3TC-LPV/r	AZT-3TC-ABC-ddl-LPV/r	ABC-3TC-AZT-LPV/r	Total (%)
Dermatological								
Skin rash	91	0	2	0	0	0	0	93 (65.5%)
Gastrointestinal								
Vomiting	8	2	0	2	4	1	2	19 (13.4%)
Nausea	0	0	0	0	3	0	2	5 (3.5%)
Diarrhea	0	0	0	0	0	2	2	4 (2.8%)
Abdominal pains	3	0	0	0	0	0	0	3 (2.1%)
Systemic manifestation								
Pallor	9	1	0	1	0	1	0	12 (8.5%)
Central Nervous System								
Headache	0	0	1	0	3	0	2	6 (4.2%)
Total	111	3	3	3	10	4	8	142

Table 5: Types and frequency of adverse events to HAART regimen.

Haematological parameters	Baseline value before HAART initiation	Mean value at follow up after HAART initiation	p-value
Severe anaemia (Hb<7 gm/dl)	5/72 (6.9%)	6/72 (8.3%)	0.57
Thrombocytopenia (<100,000 mm ⁻³)	1/72 (1.4%)	2/72 (2.8%)	0.58
Macrocytosis MCV (>95 μm ⁻³)	8/72 (11.1%)	22/72 (20.6%)	0.01
Neutropenia WBC count (<1000 mm ⁻³)	None	None	-
Viral load (≤ 4000 RNA copies mL ⁻¹)	6/78 (8.0%)	8/78 (10.3%)	0.61
CD4+ count (<200/μL)	12/78 (15.4%)	11/78 (14.1%)	0.57

Table 6: Haematological adverse events based on abnormalities of laboratory results.

females (25; 65.8%) than males (13; 34.2%) experienced the adverse events.

All the 38 patients experienced a total of 142 clinical adverse events (an average of 4 AEs per patient). Table 5 shows the types and frequency of the adverse events that occurred in the patients. AZT-3TC-NVP combination was the most implicated regimen and accounted for 111 (78.2%) of the adverse events. Skin rashes accounted for over half of the adverse events and were associated with nevirapine based regimens (AZT-3TC-NVP and ABC-3TC-NVP).

Suspected laboratory adverse events to ARV drugs

The suspected haematological adverse events observed in the patients are presented in Table 6. Only 72 (90%) patients had a complete haematological results following baseline and follow up investigations. However, 78 (97.5%) patients had a complete virological results following baseline and follow up investigations. Anaemia (8.3%), macrocytosis (20.6%), and thrombocytopenia (2.8%) were the three commonest haematological adverse events observed in this study after HAART initiation. These were based on laboratory exclusion of other causes of anaemia such as iron, folate and vitamin B12 deficiencies, Glucose-6-phosphate dehydrogenase deficiency, and haemoglobinopathies.

Discussion

About 40% of the patients in this study were either moderately or severely malnourished at enrolment on HAART. Studies have shown a significant decrease in the quality and quantity of metabolizing enzymes of non-HIV infected children with severe malnutrition [16,17], suggesting their potential risks for drug toxicity. Considering the lack of data on metabolism of ARV drugs in malnourished children, HIV-infected children who are malnourished may be at higher risk of adverse drug events than their well-nourished counterparts. It is

hoped that a prospective pharmacovigilance study would address the differential effects of malnutrition on the adverse events to ARV drugs in children living with HIV.

The prevalence of adverse events to ARV drugs was 47.5% in this study. This rate was lower than the rates reported among HIV-infected adult population in India (71.1%) [18] and Nigeria (54%) [19], but higher than the rate reported in Brazil (34.5%) [20]. However, a similar rate (45%) has been reported in a large cohort study of HIV-infected adults in Switzerland [21]. This suggests that the spectrum of adverse events to ARV drugs vary from one country to another and between developed and developing countries. The variations in the rates may be explained by the differences in the methodology of the studies, the population studied, the HAART regimens prescribed, and the definition of adverse event used in each study. While we performed a retrospective study, most of the other studies were prospective. Except the SWISS study, other studies claimed that the rates reported were for adverse reactions to ARV drugs without performing any causality assessment.

The tendency to experience adverse events to ARV drugs is highest in the first six months after HAART initiation [19]. The early occurrence of AEs was explained by Duval et al. [22] as an expression of intrinsic intolerance rather than delayed toxic accumulation process. Over half of the AEs reported in this study were experienced within 3 months of HAART initiation. This is similar to the onsets of AEs reported in other studies [18,20]. Nevirapine-associated rash was the commonest clinical adverse event that occurred in this study and did not require a major therapeutic intervention. The prevalence of skin rashes (65.5%) reported in our study was similar to the rate reported in HIV-infected adult population in Northern Nigeria [23] but occur less frequently and less severely than previously reported among HIV-infected children in Jamaica [24] and the United Kingdom [25]. However, the prevalence

was higher than the rate reported in India [26]. Over 90% of the patients involved in this study were on a nevirapine-based regimen, part of the recommended first-line paediatric HAART regimen in Nigeria. The low prevalence of nevirapine-hypersensitivity and its gradual decrease over the first 12 months of therapy substantiates the continual use of this regimen for ARV initiation.

Anaemia, presenting with pallor, is a common adverse event to HAART regimen and it is associated with zidovudine [24,26]. Despite all our patients receiving a zidovudine-based HAART regimen, only 8.3% showed clinically significant anaemia which necessitated a change to a second-line HAART regimen in one patient. This was lower than the 12-16% reported in Jamaica [24] and India [26]. A clinically significant anaemia was based on the haemoglobin concentration and defined, in accordance to previous studies, as mild (9-9.9 gm/dl), moderate (7-8.9 gm/dl), and severe (<7 gm/dl) [1,7]. However, none of the patients experienced a life threatening anaemia that would necessitate blood transfusion. Close monitoring and pharmacovigilance is therefore crucial for early detection and timely intervention in the management of life threatening anaemia in HIV-infected children on zidovudine-based HAART regimen.

Macrocytic anaemia associated with zidovudine is common in HIV-infected children [24] and adult [27]. We reported a prevalence of 30.6% for macrocytic anaemia in this study, similar to the 30-40% reported in other studies [24,27]. Thrombocytopenia may occur as a consequence of bone marrow suppression by zidovudine. It occurred in 2.8% of our patients compared to 4-8% reported in other studies [24,27]. None of the patients presented with bleeding diatheses since their initiation on HAART regimen. In most cases, thrombocytopenia was detected on routine haematological investigation and resolved spontaneously.

Biochemical investigations were not done regularly for the patients, and among the few cases investigated, baseline and follow up data were either missing or incomplete. It was therefore difficult to assess the effect of zidovudine on the metabolic and endocrine functions of the patients involved in this study. This limitation therefore underscores the significance of a prospective pharmacovigilance in the effective monitoring of adverse events to ARV drugs in HIV-infected children.

Conclusion

Despite the limitations of this study, we found that the ARV drugs were generally safe and well tolerated with few adverse events. Most of the clinical and haematological adverse events observed were neither severe nor life threatening suggesting a good safety profile of the ARV drugs. Staff training on pharmacovigilance of ARV drugs, institution of a detailed questionnaire to elicit pertinent adverse events of ARV drugs, and adequate documentation of laboratory results could improve monitoring of adverse events associated with the use of ARV drugs in a resource limited country like Nigeria.

References

1. UNAIDS (2011) World AIDS Day Report.
2. AIDS at 30 (2011) Nations at the crossroads.
3. U.S. Global Health Policy. The global HIV/AIDS epidemics, November 11-Factsheet.
4. World Health Organization (2006) Antiretroviral therapy of HIV infection in infants and children: towards universal access. WHO, Geneva.
5. Jordan R, Gold L, Cummins C, Hyde C (2002) Systematic review of meta-analysis of evidence for increasing numbers of drugs in antiretroviral combination therapy. *BMJ* 324: 1-10.
6. Levin LJ (2005) Changing antiretroviral therapy in paediatric patients. *South Afr J HIV Med* 6: 38-42.
7. Uzochukwu BS, Onwujekwe OE, Onoka AC, Okoli C, Uguru NP, et al. (2009) Determinants of non-adherence to subsidized anti-retroviral treatment in southeast Nigeria. *Health Policy Plan* 24:189-196.
8. Montessori V, Press N, Harris M, Akagi L, Montaner JS (2004) Adverse effects of antiretroviral therapy for HIV infection. *CMAJ* 170: 229-238.
9. Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N (2007) Adverse effects of highly active antiretroviral therapy in developing countries. *Clin Infect Dis* 45: 1093-1101.
10. Borrás-Blasco J, Navarro-Ruiz A, Borrás C, Castera E (2008) Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. *J Antimicrob Chemother* 62: 879-888.
11. Brown BJ, Oladokun RE, Odaibo GN, Olaleye DO, Osinusi K, et al. (2011) Clinical and immunological profile of paediatric HIV infection in Ibadan, Nigeria. *J Int Assoc Physicians AIDS Care (Chic)* 10: 49-53.
12. Adejuyigbe EA, Oyelami O, Onayemi O, Durosinmi MA (2003) Paediatric HIV/AIDS in Ile-Ife, Nigeria. *Cent Afr J Med* 49: 74-78.
13. Adetifa IM, Temiye EO, Akinsulie AO, Ezeaka VC, Iroha EO (2006) Haematological abnormalities associated with paediatric HIV/AIDS in Lagos. *Ann Trop Paediatr* 26: 121-125.
14. Reddi A, Leeper SC, Grobler AC, Geddes R, France KH, et al (2007) Preliminary outcomes of paediatric highly active antiretroviral therapy cohort from KwaZulu-Natal, South Africa. *BMC Paediatr* 7: 13.
15. WHO Multicentre Growth Reference Study Group (2006) WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl* 450: 76-85.
16. Oshikoya KA, Senbanjo IO (2009) Pathophysiological changes that affect drug disposition in protein-energy malnourished children. *Nutr Metab (Lond)* 1: 6:50.
17. Oshikoya KA, Sammons HM, Choonara I (2010) A systematic review of pharmacokinetics studies in protein-energy malnutrition. *Eur J Clin Pharmacol* 66: 1025-1235.
18. Sharma A, Vora R, Modi M, Sharma A, Marfatia Y (2008) Adverse effects of antiretroviral treatment. *Indian J Dermatol Venereol Leprol* 74: 234-237.
19. Eluwa GI, Badru T, Akpoigbe KJ (2012) Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria. *BMC Clin Pharmacol* 12: 7.
20. Pádua CA, CéSAR CC, Bonolo PF, Acurcio FA, Guimarães MD (2006) High incidence of adverse reactions to initial antiretroviral therapy in Brazil. *Braz J Med Biol Res* 39: 495-505.
21. Keiser O, Fellay J, Opravil M, Hirsh HH, Hirshel B, et al. (2007) Adverse events to antiretrovirals in the Swiss HIV Cohort Study: effect on mortality and treatment modification. *Antivir Ther* 12: 1157-1164.
22. Duval X, Journot V, Lepout C, Chêne G, Dupon M, et al. (2004) Incidence of and risk factors for adverse drug reactions in a prospective cohort of HIV infected adults initiating protease inhibitor containing therapy. *Clin Infect Dis* 39: 248-255.
23. Obiako OR, Haruna MM, Sani GB, Tobi-Ajayi E, Adebola OT, et al. (2012) Adverse reactions associated with antiretroviral regimens in adult patients of a university teaching hospital HIV program in Zaria, Northern Nigeria: an observational cohort study. *J Antivir Antiretrovir* 4: 6-13.
24. Pryce C, Pierre RB, Steel-Duncan J, Evans-Gilbert T, Palmer P, et al. (2008) Safety of antiretroviral drug therapy in Jamaican children with HIV/AIDS. *West Indian Med J* 57: 238-245.
25. Verweel G, Sharland M, Lyall H, Novelli V, Gibb DM, et al. (2003) Nevirapine use in HIV-1- infected children. *AIDS* 17: 1639-1647.
26. Shah I (2006) Adverse effects of antiretroviral therapy in HIV-1- infected children. *J Trop Pediatr* 52: 244-248.
27. Fischl MA, Parker CB, Pettinelli C, Wulfsohn M, Hirsch MS, et al. (1990) A randomized controlled trial of a reduced daily dose of Zidovudine in patients with the Acquired Immunodeficiency Syndrome. *N Engl J Med* 323: 1009-1014.